NIH Blueprint for Neurotherapeutics: A novel approach to early stage drug discovery research funding

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NINDS
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Program Vision
Combine Strengths of NIH and Industry

**NIH investigator-initiated ideas**
- Novel drug targets
- Strong disease assays and models

**Industry expertise**
- Advisors with extensive pharma experience
- Industry-standard contract services
Blueprint Neurotherapeutics Network
Offering Infrastructure, Expertise, and Funding

Lead Development Team

Principal Investigator*
Industry-seasoned consultants
NIH staff

*PI retains intellectual property

Medicinal Chemistry

Data Management

PK/Tox

SOUTHERN RESEARCH INSTITUTE

Formulation/Manufacturing

Bioactivity/Efficacy Studies

TBD Jan. 2015

TBD 2016

Phase I Clinical Trials

TBD Jan. 2015

TBD 2016
BPN Consultants

- **Assay development, pharmacology**
  - Lisa Minor
  - Bill Martin
  - Vince Groppi
  - Jeff Conn
  - Bryan Roth

- **Medicinal chemistry**
  - Graham Johnson
  - Donna Romero
  - Neil Moss
  - Paul C. Anderson
  - Steve Young
  - John McCall

- **DMPK**
  - Paul Pearson
  - Jiunn Lin
  - Ron White

- **Toxicology**
  - Marc Bailie
  - TBD

- **Development**
  - Peter Farina
  - Mike Detke
  - Gian Luca Araldi
  - Jon P. Lawson
  - John M. “Jay” Sisco

- **Regulatory affairs**
  - TBD

See bios at [http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm](http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm)
Goal: Advance Projects for Hand-Off

- Strong biological validation
- Stage-appropriate compounds
- No IP constraints

Risk decreases as projects successfully advance
Projects are Milestone-Driven
External Review Committee Assesses Progress Biannually

Projects Launched

High attrition rate anticipated

Exploratory Studies
Optimization Chemistry
Pre-clinical safety testing
Human safety testing (Phase I)

New drug candidates licensed

Milestones
Validated Assays
Emerging SAR

External Review Committee
Peter Farina, PhD (chair)
Jeffrey Conn, PhD
Michael J. Detke, MD, PhD
John McCall, PhD
Bryan Roth, MD, PhD
Confidentiality and IP Protection

Confidentiality
• Applications reviewed in closed (non-public) meetings
• Reviewers are under strict confidentiality agreements
• Only funded abstracts are made public
• NIH contracts with consultants, research service providers, and steering committee members include confidentiality requirements
• NIH employees are required to protect confidentiality by law

Intellectual Property
• Goal: Unencumbered IP, controlled by PI’s institution
• Consultants and chemistry contractor assign IP rights up front to the PI’s institution
• NIH has no stake in the IP
Who Applies for BPN?

- Researchers who are new to drug discovery
- Researchers who are experienced in drug discovery but lack necessary research facilities
- Academic labs and small businesses
# 15 Projects Initiated 2011-2013

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Mark Gurney</td>
<td>Tetra Discovery Partners</td>
<td>Alzheimer’s</td>
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<td>Reset Therapeutics</td>
<td>Narcolepsy</td>
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<td>Paul Kenny</td>
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<td>George Maynard</td>
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<td>Konstantin Petrukhin</td>
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<td>Susan Slaugenhaupt</td>
<td>Mass. General Hospital</td>
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<td>Steven Wagner</td>
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<td>John Bixby</td>
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<td>Raymond Dingledine</td>
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<td>Marcie Glicksman</td>
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<td>Edwin Rubel</td>
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<td>D. James Surmeier</td>
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See abstracts at [http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm](http://neuroscienceblueprint.nih.gov/bpdrugs/bpn.htm)
# Current BPN Portfolio

<table>
<thead>
<tr>
<th>Assay Validation</th>
<th>Exploratory Chemistry</th>
<th>Hit-to-Lead Chemistry</th>
<th>Proof of Concept</th>
<th>Lead Optimization</th>
<th>Candidate Selection</th>
<th>Preclinical Safety</th>
<th>Phase I Trial</th>
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*Interested in licensing opportunities?*

What’s New in BPN

• Flexibility in mix of contract access and grant support
  – Investigators choose what combination best fits their needs
  – Offers option for grant-only support

• Flexibility in entry point
  – Projects can enter during Discovery or Development

• Phased funding allows for due diligence, filling in data gaps

• SBIR track available
Projects Can Enter at Any Preclinical Stage
All Projects Begin with Preparatory Phase

- Complete entry criteria for SAR or IND-enabling studies
- Conduct due diligence

Preparatory Feasibility

Hit-to-Lead/Lead Optimization (SAR)  IND-Enabling  Phase I Trials

Discovery  Development

UH2 U44-I
General SBIR

UH3 U44-II
Examples of Preparatory Activities

Discovery Phase: Get Ready for Med Chem

• Form Lead Development Team
  – Define milestones, goals for optimization
  – Establish compound testing funnel
• Optimize, validate assays to drive SAR
• Assay correlation studies to define advancement criteria
• ADMET profiling to identify compound liabilities
• Studies to address questions on proof-of-concept
Examples of Preparatory Activities
Development Phase: Get Ready for IND-Enabling Studies

- Establishment of a preclinical development plan
- Design and planning for the first-in-human clinical trial
- Replication/confirmation of key in vivo pharmacology data
- Scale-up synthesis
- Salt and polymorph screening
- Compound stability studies
- Pre-formulation studies
- Multiple-dose rodent PK testing, with PD correlations if applicable
- Dose-range finding toxicology
- Metabolite identification
Now Accepting New Applications

- **PAR-14-293** for all applicants
- **PAR-14-292** for small businesses (SBIR)
- First applications due Oct 21, 2014
- First peer review in February 2015 (special review panel)
- First grants awarded July 2015
- For the following indications
  - Psychiatric disorders
  - Neurological disorders
  - Degenerative dementias of aging
  - Developmental disorders
  - Chronic pain conditions
  - Alcohol dependence
  - Drug addiction
Network Entry Criteria

Discovery Stage

Disease biology

- Novel target for the disease
- Strong biological validation
  - *in vivo* PD read-out desirable
  - *in vivo* efficacy not absolutely required
- Feasible path to the clinic

Assays

- Robust *in vitro* assay for optimization
- Strong confirmatory assays

Compounds

- Project must require medicinal chemistry
- Amenable to chemistry
- IP free of obvious roadblocks
Network Entry Criteria

*Development Stage*

**Fully Optimized Compound**
- Strong data linking target to disease
- Biological & ADMET activity appropriate for intended clinical use*
  - Efficacy/PD when delivered by clinically intended route
  - Fully profiled, defensible ADMET results†
- Feasible path to the clinic
- IP free of obvious roadblocks

* Must be consistent with Target Product Profile
† Must have fully completed Compound Profile Table
Budget Guidance

Grant pays for PI-led work only
  – NIH pays BPN contractors directly
  – PI may select own contractors and include in grant budget

If no BPN contracts are used,* PI may request:

• General
  – UH2: Up to $300K direct costs x 1 year
  – UH3: Up to $1.5M/year direct costs x 4 years

• SBIR
  – Phase I: Up to $400K total costs x 1 year
  – Phase II: Up to $4M total across 3 years

* If work will be conducted by BPN contractors, the grant budget should be offset accordingly

Applications $500K+ (direct) must be pre-approved by NIH staff for submission
Advice for Preparing an Application

• Contact NIH staff
  - Confirm which entry stage is best fit
  - Discuss activities for Preparatory Phase
  - Applications $500K+ must be preapproved to submit

• Read the FOA (this isn’t a typical NIH application)
• Show the data for assay validation, target validation, etc.

See FAQs at http://neuroscienceblueprint.nih.gov/bpdrugs

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